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The natural variability in asthma

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Summary

The results of the studies presented in this thesis have contributed to a further understanding of the management of asthma. The two clinical models, nocturnal airflow limitation and allergen challenge, were very useful to unravel the differences in pharmacological properties of Fluticasone Propionate (FP) and Salmeterol Xinaphoate (SLM) and their implications for the clinical setting.

Nocturnal asthma symptoms are a clinical expression of nocturnal airflow limitation and a circadian variation in Peak Expiratory Flow (PEF) of more than 15% is considered to be clinical relevant. This is outlined in **chapter 2**, where it has been stated that nocturnal respiratory symptoms are the expression of asthma deterioration, instead of the separate disease entity called "nocturnal asthma". Since increase in nocturnal airflow limitation reflects the natural variability in deterioration of asthma, it needs therapeutic intervention. Although the optimal therapy strategy is unknown, (inter)national guidelines recommend addition of long-acting $ß_2$-agonists to inhaled glucocorticosteroids using on a regular base. In **chapter 3**, we have investigated different therapy approaches, which are commonly used in asthmatics with nocturnal airflow limitation. In 46 atopic asthmatics, all with a circadian PEF variation of $\geq$ 15%, we have compared 250 µg bd of FP with 50µg bd of SLM and with the combination of these both drugs. This was a short-term study of 6 weeks. By using different lung function tests, all associated with nocturnal airflow limitation, one may distinguish different therapeutic effects, which can be clinical relevant.The three treatment approaches showed a comparable therapeutic effect in improving of the generally used clinical outcome parameters. All three approaches reduced circadian PEF variation below 10% and increased FEV_1 at day and night above 90% predicted. Furthermore, they all decreased PC_{20} MCh with at least 1.5 doubling concentrations and dampened the nocturnal decline in PC_{20} MCh, except for the combination arm. So far, it seemed that SLM as monotherapy might be as effective as FP as monotherapy and their combination. However, FP and their combination appeared to have superior beneficial effects when assessed by PC_{20} AMP. SLM as monotherapy showed a less marked improvement in PC_{20} AMP than when added to FP. Therefore, studies comparing different treatment approaches and using outcome parameters such as PEF, FEV_1 and BHR to direct stimuli like methacholine have to be carefully interpreted. This study is the first one, which gives support to the formal recommendation as suggested by (inter)national guidelines.

Nocturnal symptoms, especially nocturnal awakenings, influence daytime cognitive performance. In **chapter 4**, we have shown that a high level of circadian PEF varia-

tion >20% was associated with a lower level of daytime cognitive performance in atopic asthmatics. A battery of psychometric tests was used to assess cognitive performance. These consisted of Stroop Color Word test, Trail making A and B, and the PASAT test, assessing focused attention and concentration. Sixteen healthy volunteers served as control group. In the group of 46 atopic asthmatics significantly lower scores were observed compared to these healthy volunteers. The cognitive performance level improved up to the level of the healthy volunteers after 6 weeks of therapeutic intervention with FP 250µg bd or SLM 50µg bd or their combination, no matter which therapy was used. This improvement was accompanied by a mean reduction in circadian PEF variation to below 10%. Our results may open a new way for investigations since lower daytime cognitive performance, especially in young children with asthma at school age, may interfere with school- and work performances. Our findings showed that therapeutic intervention of nocturnal airflow limitation is important to reduce asthma deterioration and to improve the cognitive function level of asthmatics. Further it seems important to validate these findings in older people with COPD as well.

In **chapter 5**, we investigated the pathophysiologic implications of inhaled glucocorticosteriods (FP) and long-acting ß$_2$-agonists (SLM) with respect to their decrease of bronchial hyperreponsiveness (BHR) to both stimuli, a directly acting one methacholine (MCh) and an indirectly acting one i.e. adenosine 5'-monophosphate (AMP). Thirtyfour atopic asthmatics were treated with either FP 250µg bd or SLM 50µg bd for 6 weeks. FP resulted in a significantly larger improvement in PC_{20} AMP (5±1.1DC, Doubling Concentrations) compared to SLM (2.2±0.9 DC). FP resulted in a comparable improvement in PC_{20} MCh (2.2±0.4 DC) compared to SLM (1.4±0.5 DC). FP induced a significantly larger improvement in PC_{20} AMP compared to PC_{20} MCh (Δ2.7±1.0 DC), which was less marked for SLM (Δ0.8±0.7 DC). In addition to improvement in BHR, both drugs increased comparably the FEV_1-values. Since it has been shown that geometric airway factors are associated with BHR to MCh, it is intriguing whether improvement in FEV_1 might lead to a partial improvement in BHR either assessed with MCh or AMP. In the present study, we observed only a positive correlation between FP-induced improvement in FEV_1 and BHR to MCh. But we observed neither a correlation between SLM-induced improvement in FEV_1 and improvement in BHR to MCh, nor between these two drug-induced improvements in FEV_1 and improvement in BHR to AMP.
Airway diameter may be improved by different geometric airway factors such as a decrease of airway wall thickness, which includes reduction of oedema and infiltrating inflammatory cells, or a reduction of pre-existent airway smooth muscle tone, or a modulation of the extracellular matrix structure. It is tempting to speculate that FP

improves the airway diameter by modulation of airway wall oedema, inflammatory cell infiltration, and pre-existent airway smooth muscle tone as geometric airway factors in order to improve BHR to MCh. The enhanced FP-induced improvement in BHR to AMP compared to BHR to MCh, with no positive correlation between airway diameter and improvement in BHR to AMP, suggests that other mechanisms are important for its action as well. Therefore, we hypothesize that the improvement in BHR to AMP by FP seems to be related to reduction in mast cell numbers and increase in stability of these cells and to a minor or no extent to airway wall thickness. Since no correlation was observed between SLM-induced increase in FEV_1 and improvement in BHR to MCh reduction of pre-existent airway smooth muscle tone by SLM seems not an important determinant of improvement in BHR to MCh after SLM use. Furthermore after SLM use, BHR to MCh was improved comparably to BHR measured with AMP. Both findings strengthen the opinion that SLM has prolonged bronchoprotective activities based on sustained functional antagonism.

In **chapter 6**, we introduced a new $ß_2$-agonist, picumeterol that was short-acting in the clinical setting, as assessed by FEV_1. This was at odds with their long-acting activity in *in vitro* and in animal studies. This suggests species differences in response to $ß_2$-adrenoceptor stimulation by this compound. The pharmacological properties of picumeterol being highly potent in increasing intracellular c-AMP, but of apparently low intrinsic activity. This is, therefore, a picture of a clear partial agonist. The results of this study showed a clear increase in FEV_1 and no significant reduction of BHR to MCh after inhalation of a single dose of picumeterol, which might be due to this partial agonism. It is known that an increase in intracellular c-AMP is necessary for airway smooth muscle relaxation and for counteracting bronchospastic exogenous and endogenous stimuli. Most likely, picumeterol increased intracellular c-AMP to a level sufficient for increasing FEV_1, but insufficient to reverse MCh-induced bronchoconstriction.

Natural allergen exposure, which leads to asthmatic inflammation of the airway wall is simulated by an allergen challenge in the laboratory. The underlying pathophysiologic mechanisms are outlined in **chapter 7**. The early asthmatic response is associated with release of bronchospastic mediators by IgE-triggered mast cells resulting directly in airway narrowing and resolving within an hour. This response is followed by a late asthmatic response within hours which is sustained for more than 12 hours and associated with an increase in BHR. Naturally occurring diurnal variation in airway tone may interfere with the detection of the late asthmatic response, thereby dampening the response. Therefore, a control challenge with saline should always be performed prior to an allergen challenge, in order to correct confounders.

With the introduction of long-acting $ß_2$-agonists, other pharmacological properties were envisaged including anti-inflammatory effects in addition to prolonged bronchodilation. This was based on many *in vitro* studies and some *in vivo* studies, which were inconclusive as to whether the long-acting $ß_2$-agonists have clinically important anti-inflammatory properties. We investigated the protective effects of a single dose of 50µg SLM on the allergen-induced asthmatic response in **chapter 8**. This study has shown that SLM completely inhibited the fall in FEV_1 up to 10 hours after the house dust mite challenge. However, we performed a control challenge and applied corrections for confounders, i.e. the bronchodilator properties of SLM and the spontaneous diurnal variation in airway diameter. After these corrections, a biphasic dampened asthmatic response was observed, and a fall in FEV_1 of more than 20% was detected 10 hours after the house dust mite challenge. Furthermore, SLM reduced the allergen-induced increase in BHR 3 hours after challenging, but no reduction was observed after 24 hours. It is clear that a single dose of SLM modifies the early and late asthmatic response, but this is particularly due to its prolonged bronchodilator and bronchoprotective activities.

In atopic asthmatics, the IgE-mediated allergic response contributes to the asthmatic inflammation of the airway wall. In this response, T cells play a central role. Only the T cell antigen receptors (TCR) recognize and bind oligopeptide fragments of allergens accompanied by MHC-class II molecule. TCR responses to allergens may be oligoclonal, as characterized by use of a limited set of Vα and Vß gene families with conservation of junctional region lengths. We investigated in **chapter 9** the effect of segmental ragweed challenge on levels of Vα and Vß gene expression and TCR clonality of both blood and BAL fluid T cells, including T-helper and T-suppressor cells. At baseline and 24 hours after ragweed challenge, most Vα and Vß gene families were expressed in a polyclonal manner, as assessed by multiple TCR junctional region lengths using RT-PCR technique and associated with each V gene. This indicates that the TCR repertoire is diverse in atopic asthmatics even after exposure of ragweed. Polyclonal changes in the TCR repertoire of T-helper and T-suppressor cells as answer on ragweed, reflect mechanisms governing T cell recruitment and retention. In contrast, oligoclonal changes in TCR repertoire were observed in both T-helper and T-suppressor cells, thus both types of T cells recognize ragweed allergens. The unexpected finding that T-suppressor cells were involved as well in the late asthmatic reaction response could suggest that they may provide a beneficial down-regulatory effect in this response.